

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kirk Hogan
Serial No.: 09/613,887 Group No.: 1634
Filed: 07/11/00 Examiner: J.A.. Goldberg
Entitled: **Methods and Compositions for Perioperative Genomic Profiling**

**DECLARATION OF DOUGLAS BAIRD COURSIN, M.D.
UNDER 37 C.F.R. §1.132**

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.o. Box 1450, Alexandria, VA 22313-1450

Dated: 6-11-07

By: 

Mary Ellen Waite

Dear Madam:

I, Douglas Baird Coursin, M.D., do hereby declare as follows:

1. I received an M.D. in 1976 from Albany Medical College. I am a Diplomate of the National Board of Medical Examiners, the American Board of Internal Medicine, and the American Board of Anesthesiology with a Special Certificate of Competence in Critical Care Medicine. I am a Professor of Anesthesiology and Internal Medicine at the University of Wisconsin School of Medicine and Public Health. In 1996 – 1997, I served as President of the American Society of Critical Care Anesthesiologists. I've been an elected member of the Board of Directors of the American Board of Anesthesiology since 2001. I presently serve on the editorial boards of Current Opinions in Anaesthesiology, The Mayo Clinic Proceedings, and Critical Care Medicine. I am the 2006 recipient of the American Society of Critical Care Anesthesiologists Lifetime Achievement Award.
2. I understand that methodology for perioperative genomic profiles is disclosed and claimed in the patent application in connection with which this declaration is being submitted. The perioperative genomic profiles of the present patent application represent a completely novel approach that is not obvious in view of existing technologies. To my

knowledge, no one previously proposed or disclosed perioperative genomic profiles that would be successful in screening a patient perioperatively to determine a risk for multiple complications during a surgical procedure.

3. I have been in the practice of Anesthesiology and Critical Care Medicine for 26 years. During this entire time, and well before, the overriding mission of anesthesiologists, surgeons and other caregivers in the perioperative period has been to reduce the risk of adverse outcomes to the minimum for each patient. As well, it has long been recognized that inborn predispositions are significant contributors to morbidity and mortality in the interval surrounding surgery. Despite this heightened level of vigilance, and intense focus on a shared mission, no one taught or suggested perioperative genomic profiles before the present patent application.

4. Prior to the perioperative genomic profiles of the present patent application, surgeons and anesthesiologists were highly motivated to detect multiple risks for complications during a surgical procedure associated with genetic variations. For example, every patient is asked whether any family members may have had complications with surgery and anesthesia, and the patient's answer is recorded on a pre-operative checklist. Nevertheless, those of ordinary skill in the art *i.e.*, anesthesiologists and surgeons, did not arrive at the solution of the presently claimed invention. Thus, the perioperative genomic profiles of the present patent application clearly fulfill a long felt, but hitherto unmet need.

5. I have participated in a recently completed NIH-funded, prospective, multi-center investigation in which perioperative genomic profiles including alleles in *BChE*, *CYP2D6*, *MTHFR*, *MTR*, *MTRR*, *CBS*, *FII*, *FV*, *B 2AR*, *HBB*, *ApoE*, *MYH7*, *FII*, *FV*, *TPMT*, *CCR5*, *TNF a*, *TNF b*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *ABC*, *ACE*, *Gender*, and *ABO*, were generated in 450 patients undergoing surgery using the technology described in the present patent application. This NIH grant focused upon the long felt but unmet needs in detection of genetic susceptibilities in the time before, during and after surgery and anesthesia.

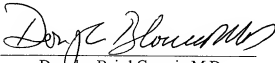
6. Surprisingly, even after polymorphisms in non-pathogenic alleles (*i.e.*, the ABO blood group and gender-specific alleles) were withdrawn from analysis, 391 of 450 patients were found to be mutant homozygotes at 1 or more loci, with a mean number of 2 mutant homozygous loci per patient. In turn, a mean of 11 mutant alleles in aggregate (*i.e.*, homozygous plus heterozygous mutant polymorphisms) per patient were observed at loci comprising the perioperative genomic panel. These unexpected results demonstrate that significant genetic heterogeneity is present in most patients in advance of surgery that is not accounted for using contemporary tools for detection, *e.g.*, a family history check-box. Without question, the perioperative genomic profiles of the present patent application will avoid many deleterious outcomes, and save lives.

7. I am aware that the perioperative genomic profiles of the present patent application have been considered obvious by the United States Patent Office in the light of numerous separate references brought together for the first time in the present application. However, if the perioperative genomic profiles of the present patent application were obvious, the ordinary

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practitioner would have arrived at the claimed combinations in view of long felt and unmet needs to directly identify genetic predispositions before, during and after surgery. No person having ordinary skill in the art, or even extraordinary skill, took this step before the claimed invention was made.

The undersigned declares further that all statements made herein of his own knowledge are true, and all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are so made punishable by fine or imprisonment, or both, under §101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: June 10th, 2007 Signed: 
Douglas Baird Coursin M.D.